Citation:

Kabat GC, Shikany JM, Beresford SA, Caan B, Neuhouser ML, Tinker LF, Rohan TE. Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes Control.* 2008 Dec;19(10):1291-8. Epub 2008 Jul 10.

PubMed ID: 18618276

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the association of intake of carbohydrates, glycemic index, glycemic load, and related dietary factors to colorectal cancer, and subsites within the colorectum, using the database of the Womens' Health Initiative Observational Study and Clinical Trial.

Inclusion Criteria:

- Postmenopausal women (ages between 50 and 79) representing major racial/ethnic groups

Exclusion Criteria:

- Missing information on colorectal cancer as an outcome
- Cases of colorectal cancer with histologies other than adenocarcinoma
- Prior history of rectal cancer
- Cancer of the appendix
- Cause of death was recorded as colorectal cancer but who had no report of incident colorectal cancer
- Women with extreme energy intakes (<600 or >5,000 kcal/day)
- Women with BMI of less than 15 or more than 50 kg/m^2

Description of Study Protocol:

Recruitment : Women's Health Study - The subjects were recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998.

Design: Prospective Cohort Study

Blinding used (if applicable): Colorectal cancer diagnoses confirmed by blinded review.

Intervention (if applicable):

Participants in the clinical trials: low-fat dietary pattern; calcium plus vitamin D supplementation; administration of estrogen alone or estrogen plus progestin

Statistical Analysis:

- Cox proportional hazard models were used to estimate hazard ratios for the association of total carbohydrate intake, glycemic index, glycemic load, and intake of total sugars and fiber, with colorectal cancer risk adjusting for colorectal cancer risk factors and potential confounding variables.
- Quintile of GI, GL, and other dietary variables of interest were computed based on the distribution in the noncases.
- Variables were included in the final models if they were established risk factors for colorectal cancer or if their inclusion altered the parameter estimate for GI or GL by more than 10%.
- When testing for trends in risk with increasing levels of the exposure of interest the corresponding median was assigned for each quintile and fitted as a continuous variable in the risk models.
- The statistical significance of the corresponding coefficient was evaluated using Wald test.
- Analyses were carried out in the observational studies (OS) and Clinical Studies (CT) with an indicator variable for OS versus CT participant.
- The main analyses were done separately for each study (OS/CT).
- Carried out sensitivity analyses were done with the exclusion of those participants in the Dietary Modification trial, women with a history of diabetes and cases of colorectal cancer diagnosed during the first two years of follow-up.
- Stratified analyses were performed within tertiles of body mass index and physical activity to detect possible effect modification by these factors.

Data Collection Summary:

Timing of Measurements:

- Demographics, medical, reproductive and family history, lifestyle factors, weight and height were collected and measured at baseline.
- Physical activity was assessed weekly.
- The self-administered FFQ was completed in the previous three months.
- Clinical outcomes were updated annually in the OS and semi-annually in the CT studies during 7.8 years.

Dependent Variables

- Colorectal cancer: the outcomes were collected by mail or telephone questionnaire
- Colorectum subsites: proximal colon, distal colon and rectum

Independent Variables

- Carbohydrate intake: self-administered FFQ designed for the WHI study inquired about usual food intake in the previous three months.
- Glycemic index and glycemic load: GI and GL database was developed and tested for use with the FFQ from the original WHI FFQ dietary database. Values for the GI of different

foods were obtained from international tables or imputed from foods with similar carbohydrate and fiber contents when published values were not available.

Control Variables

- Age
- Use of hormone therapy
- Family history of colorectal cancer
- History of diabetes
- Smoking

Description of Actual Data Sample:

Initial N: 161,800

Attrition (final N): 158,800 women (1,476 cases)

Reasons for exclusion:

- Missing information on colorectal cancer as an outcome (n=736)
- Cases of colorectal cancer with histologies other than adenocarcinoma (n=51)
- Prior history of colorectal cancer (n=951)
- Cancer of the appendix (n=1)
- Cause of death was recorded as colorectal cancer but who had no report of incident colorectal cancer (n=55)
- Women with extreme energy intakes (<600 or >5,000 kcal/day) (n=425)
- Women with BMI of less than 15 or more than 50 kg/m^2 (n=789).

Age: range 50 to 79 years; average 63 years.

Ethnicity: representing general U.S population

Other relevant demographics: The OS participants were more likely to have used hormone therapy, and had higher mean hours of total physical activity per week compared to the CT participants. In general OS and CT differ to some extent on sociodemographics, lifestyle and medical history characteristics.

Anthropometrics: BMI was lower in the OS participants.

Location: United States

Summary of Results:

- Fiber, total carbohydrates, total energy and sugar intake increased substantially, and fat intake decreased with increasing glycemic load.
- Total carbohydrate intake, glycemic index and load, plus intake of sugars and fiber showed no association with colorectal cancer, and there were no trends over increasing quintiles (HRs ranged from 0.89 to 1.16 and all 95% CI included the null value of 1.0).
- None of the hazard ratios showed any association with colorectal cancer when the OS and CT studies were analyzed separately and excluded the participants in the dietary

modification trial, those with diabetes and those excluding cases diagnosed in the first two years of follow-up.

- No associations or trends were seen for any of the carbohydrate-related variables with cancer of the proximal or distal colon.
- There was a borderline positive association of glycemic load with rectal cancer risk: HR for highest versus lowest quintile 1.84 (95% CI 0.95-3.56), P for trend = 0.05.
- No association of any of the study factors was found with BMI and physical activity

Author Conclusion:

This large study provides no evidence that a diet characterized by high glycemic index or glycemic load, or by a high intake of carbohydrate or sugars, increases the risk of colorectal cancer in generally healthy postmenopausal women.

Reviewer Comments:

Authors note the following limitations:

- *Our results may have been affected by misclassification of intake of carbohydrates and sugars due to errors of recall and changes in diet over time, or greater underreporting of diet in the cases due to higher rates of obesity*
- *Furthermore, estimates of glycemic index and glycemic load from the WHI FFQ are based on composite food groupings intended primarily to assess dietary fat; thus, estimates may not accurately reflect the glycemic effects of the individual foods or of consumption and metabolism of mixed dishes and prepared foods*
- *Glycemic index/glycemic load databases are currently incomplete*
- *Misclassification due to random variation in the computed values for glycemic index and glycemic load*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A

4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	No

7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	No
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	No
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	Yes